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PATENT- OCH REGISTRERINGSVERKET  
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## Aerosol Formulations

### Field of the Invention

- 5 The present invention relates to aerosol formulations suitable for use in metered dose inhalers (MDI's). More particularly, it relates to a formulation including a HFA propellant and a particularly suitable surface active-dispersing agent.

### Background of the invention

- 10 Drugs for treating respiratory and nasal disorders are frequently administered in aerosol formulations through the mouth or nose. One widely used method for dispensing such an aerosol formulation involves making a suspension formulation of the drug as a finely divided powder in a liquefied gas known as a propellant. Metered dose inhalers, or (MDI's) are normally used to dispense such formulations to a
- 15 patient. In an MDI, the drug is present as a finely divided, or micronised powder, in a liquefied gas known as a propellant. Surface active agents, or surfactants, are commonly included in order to aid dispersion of the drug in the propellant and to prevent aggregation of the micronised drug particles, and to improve lubrication. Surfactants work by coating the surfaces of the drug particles and so aid in wetting
- 20 the particles with the aerosol propellants.

Until recently, chlorofluorocarbon-containing propellants (CFC's) were accepted for use in all pharmaceutical aerosol formulations. Typical surfactant dispersing agents

used in the CFC-formulations were for example sorbitantriolate, oleic acid, lecithines, and ethanol. Since CFC's have been implicated in the destruction of the ozone layer, a new generation of propellants has emerged to take their place.

- 5 Hydrofluoroalkane (HFA) propellants such as 1,1,1,2-tetrafluoroethane (P134a), 1,1,1,2,3,3,3-heptafluoropropane (P227) and 1,1-difluoroethane (P152a) are today considered to be the most promising new propellants. Not only are they more "ozone-friendly", but they also have low toxicity and vapour pressures suitable for use in aerosols. However, the surfactants commonly used with the CFC formulations are
- 10 not necessarily suitable for use with the new generation of propellants. Various alternative surfactants have been proposed.

- For example, WO 92/00061 discloses polyethoxylated surfactant for use with hydrofluorocarbon propellants. WO 91/11173 discloses fluorinated surfactants. WO
- 15 91/14422 discloses perfluorinated carboxylic acid propellants for use with hydrofluorocarbon propellants. WO 92/00107 discloses the use of a 1,1,1,2-tetrafluoroethane -soluble surfactant with 1,1,1,2- tetrafluoroethane propellant.

#### Summary of the invention

- 20 It has now been found that certain specific classes of surfactant are particularly suitable for use with the new generation of propellant.

Accordingly, the present invention provides an aerosol drug formulation comprising a hydrofluoroalkane propellant or a mixture of hydrofluoroalkane propellants, a

physiologically effective amount of a drug for inhalation and a surfactant selected from a  $C_8$ - $C_{20}$  fatty acid or salt thereof, a bile salt, a phospholipid or an alkyl saccharide.

- 5 Of the fatty acids and salts thereof,  $C_8$ - $C_{16}$  such as  $C_8$ - $C_{14}$  fatty acids and salts thereof are preferred, with the salts being especially preferred. Examples of preferred fatty acid salts are sodium caprylate ( $C_8$ ), sodium, potassium or lysine caprate ( $C_{10}$ ), sodium laurate ( $C_{12}$ ) and sodium myristate ( $C_{14}$ ). As the nature of the counterion is not of special significance, any of the salts of the fatty acids are potentially useful.

10

Suitable bile salts may be for example sodium or potassium salts of cholic acid, chenodeoxycholic acid, glycocholic acid, taurocholic acid, glycochenodeoxycholic acid, taurochenodeoxycholic acid, deoxycholic acid, glycodeoxycholic acid, taurodeoxycholic acid, lithocholic acid, and ursodeoxycholic acid.

15

Of the bile salts, sodium taurocholate is especially preferred.

Suitable phospholipids may be for example single-chain phospholipids such as lysophosphatidylcholine, lysophosphatidylglycerol, lysophosphatidyletanolamine,  
20 lysophosphatidylinositol and lysophosphatidylserine or double-chain phospholipids such as diacylphosphatidylcholine, diacylphosphatidylglycerol,

diacylphosphatidyletanolamine, diacylphosphatidylinositol and diacylphosphatidylserine.

Of the phospholipids, diacylphosphatidylglycerol is preferred.

5

Suitable alkyl saccharides may be for example alkyl glucosides or alkyl maltosides, such as decyl glucoside and dodecyl maltoside.

Suitable HFA propellants are for example 1,1,1,2-tetrafluoroethane (P134a),

10 1,1,1,2,3,3,3-heptafluoropropane (P227) and 1,1-difluoroethane (P152a).

The surfactants employed in the present invention give fine dispersions in the new propellants, with good stability, and excellent bioavailability of drug dispensed from the aerosol formulations containing these surfactants.

15 In addition to drug, propellant and surfactant, a small amount of ethanol (normally up to 5% but possibly up to 20%, by weight) may be included in the formulations of the present invention. Ethanol is commonly included in aerosol compositions as it can improve the function of the metering valve and in some cases also improve the stability of the dispersion.

20

Drugs suitable for inclusion in the formulation of the present invention are any which may be delivered by inhalation. Known inhalable drugs include  $\beta$ 2-adrenoreceptor agonists such as salbutamol, terbutaline, rimiterol, fenoterol, reproterol,

- adrenaline, pirbuterol, isoprenaline, orciprenaline, bitolterol, salmeterol, formoterol, clenbuterol procaterol, broxaterol, picumeterol, TA-2005, mabuterol and the like, and their pharmacologically acceptable esters and salts; anticholinergic bronchodilators such as ipratropium bromide and the like;
- 5 glucocorticosteroids such as beclomethasone, fluticasone, budesonide, tipredane, dexamethasone, betamethasone, fluocinolone, triamcinolone, mometasone, and the like, and their pharmacologically acceptable esters and salts; anti-allergic drugs such as sodium cromoglycate and nedocromil sodium; expectorants; mucolytics; antihistamines; cyclooxygenase inhibitors; leukotriene synthesis inhibitors;
- 10 leukotriene antagonists, PLA2 inhibitors, PAF antagonists and prophylactics of asthma; antiarrhythmic drugs, tranquilisers, cardiac glycosides, hormones, anti-hypertensive drugs, antidiabetic- antiparasitic- and anticancer- drugs, sedatives and analgesic drugs, antibiotics, antirheumatic drugs, immunotherapies, antifungal and antihypotension drugs, vaccines, antiviral drugs, proteins, peptides, vitamins and
- 15 others, such as cell surface receptor blockers, antioxidants, free radical scavengers and organic salts of N,N'-diacetylcystine.

Combinations of drugs are also suitable, such as a combination of formoterol and budesonide.

20

Some drugs which are not presently available in inhalable form, such as medically or diagnostically useful peptides or proteins (collectively referred to as polypeptides) for



systemic action, including insulin, are also suitable for use in the present invention.

Polypeptides for systemic action are not today among the drugs which are administered by the aerosol route. Aerosol administration is achievable using the compositions of the present invention because the particular surfactants employed

5 have been found to have the effect of enhancing the absorption of polypeptides in the lower respiratory tract, making aerosol delivery a viable option.

The drugs may be used in the form of salts or esters or solvates (hydrates), where appropriate.

10

Other ingredients may be added into the formulation of the present invention, if desired. Such ingredients may be for example carriers, flavouring agents, buffers, antioxidants, chemical stabilisers and the like.

15 Preferably the surfactant and drug are present in the present invention in a ratio of approximately 1 : 50 to 1 : 0.2. The preferred concentration of drug in the formulations of the present invention is 0.1 mg/ml to 25 mg/ml.

20 "A drug for inhalation" means a drug which is suitable for inhalation and which consists largely of particles in a size range appropriate for maximal deposition in the lower respiratory tract (i.e., under 10 microns). The appropriate particle size range may be achieved by micronisation, which may be carried out in a suitable mill, or by

alternative methods such as spray drying or controlled crystallisation. Preferably the micronised particles range from about 0.1 to about 6 microns in diameter.

Preferably, the surfactant for use in the present invention is also in the desired particle  
 5 size range. A portion of the micronised surfactant may then be cold-mixed with a portion of the propellant and optional ethanol, whereafter the micronised drug may be added. After mixing in of the drug the remaining surfactant and propellant and optional ethanol may be added and the suspension filled into appropriate containers.

10 The invention is illustrated in the following examples.

Example 1

Sodium caprate and P134a

Sodium caprate was micronised in a jet mill. 100 mg of the substance was added to a  
 15 plastic coated glass bottle. The bottle was chilled with a mixture of carbon dioxide ice and isopropanol, and 10 ml chilled P134a was added. The bottle was sealed with a metering valve and then shaken vigorously.

A good suspension formed.

20

Example 2

Sodium caprate, insulin and P134a

Sodium caprate and insulin were micronised separately and then dry mixed. The proportion of sodium caprate to insulin was 25:75. 40 mg of this mixture was added to a plastic coated glass bottle. The bottle was chilled with a mixture of carbon dioxide ice and isopropanol, and 10 ml chilled P134a was added. The bottle was

5 sealed with a metering valve and then shaken vigorously.

A good suspension formed.

### Example 3

10 Sodium caprate, insulin and P134a

Insulin was added to a beaker with water and was dissolved. Sodium caprate was added and dissolved and the pH was adjusted to 7.4. The proportion of sodium caprate to insulin was 25:75. The solution was concentrated by evaporation of the water. The obtained solid cake was crushed, sieved and micronised in a jet mill.

15 40 mg of the powder was added to a plastic coated glass bottle. The bottle was chilled with a mixture of carbon dioxide ice and isopropanol, and 10 ml chilled P134a was added. The bottle was sealed with a metering valve and then shaken vigorously.

A good suspension formed.

20

### Example 4

Various surfactants, insulin and P134a

The procedure in Example 3 was repeated with potassium caprate (27 %), lysine caprate (35 %), sodium myristate (30 %), sodium laurate (25 %) and sodium caprylate (25 %). The quality of the suspensions was comparable with the suspension with sodium caprate.

5

#### Example 5

Sodium caprate, insulin and P227

Insulin was added to a beaker with water and was dissolved. Sodium caprate was added and dissolved and the pH was adjusted to 7.4. The proportion of sodium caprate to insulin was 25:75. The solution was concentrated by evaporation of the water. The obtained solid cake was crushed, sieved and micronised in a jet mill.

40 mg of the powder was added to a plastic coated glass bottle. The bottle was chilled with a mixture of carbon dioxide ice and isopropanol, and 10 ml chilled P227 was added. The bottle was sealed with a metering valve and then shaken vigorously.

15 An acceptable suspension formed.

#### Example 6

Various surfactants, insulin and P227

The procedure in Example 5 was repeated with potassium caprate (27 %), lysine caprate (35 %), sodium myristate (30 %), sodium laurate (25 %) and sodium caprylate (25 %). The quality of the suspensions was comparable with the suspension with sodium caprate.

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Example 7

Sodium caprate, insulin and P134a

- Sodium caprate and insulin were micronised separately and then dry mixed. The
- 5 proportion of sodium caprate to insulin was 25:75. 80 mg of this mixture was added to an aerosol vial. The aerosol vial was chilled with a mixture of carbon dioxide ice and isopropanol, and 10 ml chilled P134a was added. The aerosol vial was sealed with a 50 µl metering valve and then treated a couple of minutes in an ultra sonic bath.
- 10 The particle size of insulin in the aerosol delivered from the container was measured with an Andersen impactor at 28,3 lit/min. The fraction of fine particles was 41 % of the delivered dose. The particle measurement was repeated after storage in two months at room temperature and no deterioration was observed. The fine particle fraction was 46 %.

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Example 8

The general procedure of Example 3 was followed in the preparation of formulations of insulin with

- A. sodium taurocholate and propellant P134a
- 20 B. sodium taurocholate and propellant P227
- C. dioctanoylphosphatidylglycerol and propellant P134a
- D. dioctanoylphosphatidylglycerol and propellant P227

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Good suspensions were formed.

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## Claims

1. An aerosol drug formulation comprising a hydrofluoroalkane propellant, a physiologically effective amount of an inhalation drug and a surfactant selected from a
  - 5 C<sub>8</sub>-C<sub>20</sub> fatty acid or salt thereof, a bile salt, a phospholipid or an alkyl saccharide.
  2. An aerosol drug formulation as claimed in claim 1 in which the surfactant is a C<sub>8</sub>-C<sub>14</sub> fatty acid or salt thereof.
  - 10 3. An aerosol drug formulation as claimed in claim 2 in which the surfactant is selected from sodium caprylate (C<sub>8</sub>), sodium, potassium or lysine caprate (C<sub>10</sub>), sodium laurate (C<sub>12</sub>) and sodium myristate (C<sub>14</sub>).
  4. An aerosol drug formulation as claimed in claim 1 in which the surfactant is a bile
    - 15 salt selected from sodium or potassium salts of cholic acid, chenodeoxycholic acid, glycocholic acid, taurocholic acid, glycochenodeoxycholic acid, taurochenodeoxycholic acid, deoxycholic acid, glycodeoxycholic acid, taurodeoxycholic acid, lithocholic acid, and ursodeoxycholic acid.
    - 20 5. An aerosol drug formulation as claimed in claim 4 in which the surfactant is sodium taurocholate.

6. An aerosol drug formulation as claimed in claim 1 in which the surfactant is a phospholipid selected from single-chain phospholipids such as lysophosphatidylcholine, lysophosphatidylglycerol, lysophosphatidyletanolamine, lysophosphatidylinositol and lysophosphatidylserine or double-chain phospholipids such as diacylphosphatidylcholine, diacylphosphatidylglycerol, diacylphosphatidyletanolamine, diacylphosphatidylinositol and diacylphosphatidylserine.
7. An aerosol drug formulation as claimed in claim 6 in which the surfactant is diacylphosphatidylglycerol.
8. An aerosol drug formulation as claimed in claim 1 in which the propellant is 1,1,1,2-tetrafluoroethane (P134a), 1,1,1,2,3,3,3-heptafluoropropane (P227), or 1,1-difluoroethane (P152a) or a mixture of two or all of these.
9. An aerosol drug formulation as claimed in claim 1 additionally comprising up to 20% of ethanol.
10. An aerosol drug formulation as claimed in claim 1 in which the drug is selected from  $\beta$ 2-adrenoreceptor agonists such as salbutamol, terbutaline, rimiterol, fenoterol, reproterol, adrenaline, pirbuterol, isoprenaline, orciprenaline, bitolterol, salmeterol, formoterol, clenbuterol procaterol, broxaterol, picumeterol, TA-2005,



- mabuterol and the like, and their pharmacologically acceptable esters and salts;  
 anticholinergic bronchodilators such as ipratropium bromide and the like;  
 glucocorticosteroids such as beclomethasone, fluticasone, budesonide, tipredane,  
 dexamethasone, betamethasone, fluocinolone, triamcinolone, mometasone, and the  
 5 like, and their pharmacologically acceptable esters and salts; anti-allergic drugs  
 such as sodium cromoglycate and nedocromil sodium; expectorants; mucolytics;  
 antihistamines; cyclooxygenase inhibitors; leukotriene synthesis inhibitors;  
 leukotriene antagonists, PLA2 inhibitors, PAF antagonists and prophylactics of  
 asthma; antiarrhythmic drugs, tranquilisers, cardiac glycosides, hormones, anti-  
 10 hypertensive drugs, antidiabetic- antiparasitic- and anticancer- drugs, sedatives and  
 analgesic drugs, antibiotics, antirheumatic drugs, immunotherapies, antifungal and  
 antihypotension drugs, vaccines, antiviral drugs, proteins, peptides, vitamins, and  
 cell surface receptor blockers, antioxidants, free radical scavengers and organic  
 salts of N,N'-diacetylcystine.

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# Abstract

Aerosol formulations suitable for use in metered dose inhalers comprise a

5 hydrofluoroalkane propellant, an inhalation drug and a surfactant which is a  $C_8$ - $C_{20}$  fatty acid or salt thereof, a bile salt, a phospholipid, or an alkyl saccharide.

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